STUDY OF THE CONTAINER-INTERACTION BETWEEN ETOPHOS POLYVINYL CHLORIDE (PVC) PERFUSION

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ETOPHOS® (ETOPHOS Phosphate, 100mg)
• Etopophos® is an anticancer drug inhibiting Type II Topoisomerase, prodruk of Etoposide widely used in solid and hematological cancers in pediatric and adult population.
• It is administered by slow intravenous route, in 30 to 60 minutes injections, causing a risk of interaction with the PVC perfusion system.
• Etoposide is known for its poor solubility, its short stability and its capacity to interact with plastic components, due to the presence of Polysorbate 80 as excipient in the formulation.

AIMS
To study the interaction between Etopophos® and the PVC perfusion system in real life conditions at 3 concentrations corresponding at the extreme dosages (38mg et 580mg) and the mean one (150mg)

MATERIAL AND METHODS

RP-HPLC ➔ Analysis of plasticizers
• Mobile phase 80% Acetonitrile / 13% Methanol / 7% Water.
• Stationary phase: Column C8 Lichrospher® (250 x 4,6-5µm) – 35°C.
• Flow: 1,2ml/min / isocratic conditions.
• Run: 30 minutes.
• Detection and quantification of 4 plasticizers: TOTM, DEHT, ESBO, DINCH.

RESULTS AND DISCUSSION

- 3 different medical devices
- Identical batch numbers for each device.
- Triplicates

CHEMOTHERAPY INFUSION SET 4 ACCESS CAIR LG®
- Connector Cair LG®
  - Ref CHD496, batch number : 21H09-TCW, per : 09/07/2024
  - 1 part is dyed in yellow (DM1c), 1 is transparent (DM1)
- Connector Cair LG®
  - Ref : CHD301AL, Batch number : 21H16-TCW, per : 16/07/2024
- Named DM2 – Polymer is dyed in yellow
- Named DM3 – Polymer is transparent

Influsing controller pump MS10 Fresenius Kabi
- Ref 20728100, batch number : 84493100, per : 31/12/2023
  - Named DM3 – Polymer is transparent

Chemotherapy infusion set 4 access CAIR LG®
  - Tubing : Infusing controller pump (Fresenius Kabi).
  - Connect-2® (CAIR LG®) : connector between bag and tubing. Plasticized with triethylhexyl trimellitate (TOTM) and/or DINCH.

PVC PERFUSION ANALYSIS

- 3 kinds of additives identified in the tubes:
  - Yellow coloring, present in DM1c et DM2, one peak eluted at rt = 3,349min.
  - TOTM : presents in all tubes, two peaks (TOTM 1 and TOTM 2) eluted respectively at rt 1 = 6,84 ± 0,064min and rt 2 = 12,49 ± 0,076min.
  - DINCH : presents in DM1, DM1c and DM2, one unique peak eluted at rt = 9,05 ± 0,027min.

No evidence of Etopophos® or Etoposide in chromatograms.

In the same way, no traces of plasticizers were detected at t0 (time of preparation), t1h (after infusing of chemotherapy through tubes) or t12h after contact.

CONCLUSION

- In real conditions study. Chemotherapies were infused at same concentration and duration than accurate chemo protocols.
- No interaction was detected between PVC and Etopophos®, or PVC and Etoposide.
- DM1 and DM2, that are medical devices designed for chemotherapy drug administrations suffer less changes than DM3 that is design for unspecific use.
- A static contact study on the same medical devices and drugs confirmed the results. There were no visible release of plasticizers in the chemotherapy and, on the opposite, no sorption of chemotherapies on the PVC tube have been demonstrated yet. That second result confirms the absence of interaction between PVC and Etoposide or Etopophos®.

Table 1 : Dosing of Etopophos® and Etoposide with Qcrx® (mg/mL)

<table>
<thead>
<tr>
<th></th>
<th>DM1</th>
<th>DM1c</th>
<th>DM2</th>
<th>DM3</th>
</tr>
</thead>
<tbody>
<tr>
<td>38mg</td>
<td>4,04</td>
<td>3,35</td>
<td>3,16</td>
<td>2,93</td>
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<tr>
<td>150mg</td>
<td>4,00</td>
<td>3,67</td>
<td>3,31</td>
<td>3,14</td>
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<tr>
<td>580mg</td>
<td>4,03</td>
<td>3,67</td>
<td>3,31</td>
<td>3,14</td>
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</tbody>
</table>

Table 2 : Concentration plasticizers (mg/mL) dosed by RP-HPLC

<table>
<thead>
<tr>
<th></th>
<th>TOTM 1</th>
<th>TOTM 2</th>
</tr>
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<tbody>
<tr>
<td>DM1</td>
<td>1,9</td>
<td>1,81</td>
</tr>
<tr>
<td>DM1c</td>
<td>1,41</td>
<td>1,53</td>
</tr>
<tr>
<td>DM2</td>
<td>1,41</td>
<td>1,36</td>
</tr>
<tr>
<td>DM3</td>
<td>0,0</td>
<td>0,0</td>
</tr>
</tbody>
</table>

Table 3 : Comparison of average plasticizers concentrations accord to contact with chemotherapy

- DM1: Highest concentration of DINCH and lowest in TOTM.
- DM1c and DM2 : DINCH et TOTM ; For colored devices, the concentration of plasticizer.
- NaCl Bags: concentration of plasticizers and colorants lower than other conditions ➔ Effect of a bigger volume infused ?
- Bags of Etoposide and Etopophos® : few variations and few significant differences.
- The tube MS10 (DM3), a device non specially design for chemotherapy administrations, but used for many drug administrations, have more changes than other tubes after the contact with chemotherapies.

Tableau 1 : Dosage of Etopophos® and Etoposide with Qcrx® (mg/mL)

<table>
<thead>
<tr>
<th></th>
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<th>Etoposide</th>
<th>NaCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM1</td>
<td>1,9</td>
<td>1,81</td>
<td>1,3</td>
</tr>
<tr>
<td>DM1c</td>
<td>1,41</td>
<td>1,53</td>
<td>1,12</td>
</tr>
<tr>
<td>DM2</td>
<td>1,41</td>
<td>1,36</td>
<td>1,28</td>
</tr>
<tr>
<td>DM3</td>
<td>0</td>
<td>0</td>
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